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In Vitro Activities of Peptide Deformylase Inhibitors against Gram-Positive Pathogens

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The activities of six peptide deformylase (PDF) inhibitors against 107 respiratory tract pathogens were studied and compared to those of ciprofloxacin and amoxicillin-clavulanate. Against *Streptococcus pneumoniae*, BB-83698 and BB-83815 were the most active PDF inhibitors (MIC at which 90% of the organisms tested were inhibited [MIC_{90}], 0.25 μg/ml). Five of the agents showed similar activity against *Moraxella catarrhalis* (MIC_{90}, 0.12 μg/ml). All PDF inhibitors were less active against *Haemophilus influenzae*; BB-3497 was the most active agent (MIC_{90}, 2 μg/ml). Five agents were studied against *Chlamydia* spp. and showed activity similar to that of ciprofloxacin (MIC, 0.5 to 4 μg/ml). This study demonstrates that PDF inhibitors have the potential to be developed for the treatment of respiratory tract infections.

Peptide deformylase (PDF) is a necessary enzyme in bacterial protein synthesis. Following translation, the *N*-formyl group is hydrolyzed by PDF. The gene encoding PDF (*def*) is present in all pathogenic bacteria but has no mammalian counterpart. Recently, two novel PDF inhibitors (BB-3497 and VRC 483) were described (1; D. Cheu, D. Patel, C. Wu, et al., Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1794, p. 333, 1999) and shown to be active against a range of gram-positive pathogens. Here we describe the activities of five new agents of the same class (including BB-3497) which, unlike VCR 483, are synthetically derived and were obtained from British Biotech Pharmaceuticals (Oxford, United Kingdom). Their activities were compared with those of ciprofloxacin (Bayer Pharmaceuticals, Basingstoke, United Kingdom) and amoxicillin-clavulanate and penicillin (GlaxoSmithKine, Worthing, United Kingdom).

A total of 107 organisms (Tables 1 and 2) were tested by methods previously described (2, 3). Briefly, susceptibility was determined by a standard agar plate dilution method with Iso-Sensitest agar (pH 7.2; Unipath, Basingstoke, United Kingdom) supplemented with 5% horse blood (Bradsure Biologicals, Loughborough, United Kingdom) and 20 mg of NAD (Sigma Chemicals, Poole, United Kingdom)/liter. The inoculum was 10^4 CFU/spot, and incubation was done for 20 h in air and 4 to 6% CO_2. The MIC was defined as the lowest concentration of antimicrobial agent at which no more than two colonies were observed. Amoxicillin and clavulanate were combined at a ratio of 2:1, and the MIC for the combination was recorded in terms of the amoxicillin MIC. *Chlamydia* spp. were studied by the method of Webberly et al. (2). Because of a limited supply of compounds, the highest concentration of the PDF inhibitors used was 16 μg/ml.

Table 1 shows the activities of the six new compounds against the bacterial strains studied. Eleven strains of *Streptococcus pneumoniae* were known to have intermediate susceptibility to penicillin (MICs, ≥0.25 and ≤1 μg/ml), one strain was resistant to penicillin (MIC, 2 μg/ml), and five had reduced susceptibility to ciprofloxacin (MIC, ≥8 μg/ml). The PDF inhibitor activities ranged from an MIC_{90} (MIC at which 90% of

TABLE 1. Activities of new compounds against bacterial strains

Organism (no. of strains) and antibiotic[a]	MIC (μg/ml)		
	50%	90%	Range
Streptococcus pneumoniae (40[b])			
BB-3497	8	≥16	2–>8
BB-83698	0.25	0.5	0.12–0.5
BB-83815	0.5	0.5	0.12–0.5
BB-83857	0.5	1	0.12–1
BB-84416	1	2	0.25–4
BB-84518	1	2	0.25–2
Penicillin	0.015	1	0.008–2
Ciprofloxacin	1	8	0.5–128
AMC	0.015	1	0.008–1
Moraxella catarrhalis (29)			
BB-3497	0.06	0.12	0.015–0.12
BB-83698	0.06	0.12	0.015–0.12
BB-83815	0.06	0.12	0.03–0.12
BB-83857	0.06	0.12	0.015–0.12
BB-84416	0.12	0.25	0.06–0.25
BB-84518	0.06	0.12	0.015–0.12
Ciprofloxacin	0.03	0.06	0.03–0.06
AMC	0.03	0.12	0.008–0.12
Haemophilus influenzae (35)			
BB-3497	0.25	2	0.06–8
BB-83698	8	≥16	0.5–≥16
BB-83815	8	≥16	0.25–≥16
BB-83857	8	≥16	0.5–≥16
BB-84416	8	≥16	0.25–≥16
BB-84518	1	4	0.06–≥16
Ciprofloxacin	0.008	0.015	0.004–1
AMC	0.5	1	0.12–16

[a] AMC, amoxicillin-clavulanate.
[b] Including 11 strains with intermediate susceptibility to penicillin, 1 strain with high resistance to penicillin, and 5 strains with reduced susceptibility to ciprofloxacin (see the text for details).

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TABLE 2. MIC and minimum lethal concentration (MLC) of ciprofloxacin and five PDF inhibitors for three *Chlamydia* strains

Antimicrobial agent	Result (μg/liter) for:					
	C. pneumoniae TW183		*C. trachomatis* CT815		*C. trachomatis* CT712	
	MIC	MLC	MIC	MLC	MIC	MLC
Ciprofloxacin	2	2	2	4	2	2
BB-3497	2	4	0.25	0.5	0.25	0.25
BB-83698	0.5	0.5	0.25	2	4	8
BB-83815	1	1	1	4	1	4
BB-83857	0.5	0.5	1	1	0.5	1
BB-84416	1	1	2	4	0.5	2

the organisms tested were inhibited) of 0.5 μg/ml for BB-83698 and BB-83815 to an MIC_{90} of >8 μg/ml for BB-3497. There was no evidence of cross-resistance between the PDF inhibitors and penicillin or ciprofloxacin. Those strains which were more susceptible to one PDF inhibitor were similarly more susceptible to the other agents of this class.

Less variation among the new agents tested was seen for *Moraxella catarrhalis*. For this organism, BB-3497 was as active as the other agents. Generally, all the compounds were as active as ciprofloxacin and amoxicillin-clavulanate.

Against *Haemophilus influenzae*, there was considerable variation among the PDF inhibitors tested, with BB-3497 being the most active, BB-84518 showing intermediate activity, and the remaining compounds being markedly less active. There was no link between lack of susceptibility to amoxicillin-clavulanate and that to the PDF inhibitors.

In Table 2, the activities of five of the PDF compounds against three strains of *Chlamydia* spp. are shown and compared with that of ciprofloxacin. Generally, the new agents displayed activities similar to that of the fluoroquinolone, and BB-83857 was the most consistently active compound.

In this study, one agent, BB-3497, whose structure has been described in patent application WO99/39704 (1), was shown to be less potent against respiratory pathogens than the other five compounds studied. The exception was the greater activity of BB-3497 against *H. influenzae*; whereas the range of MICs of the new compounds against *S. pneumoniae* and *M. catarrhalis* was moderately narrow, a far greater degree of activity was noted against *H. influenzae*. It is not known if this result is related to differences in the avidities of the PDF inhibitors for the target sites or is related to bacterial cell penetration.

An earlier study (1) showed that BB-3497 is active when given orally and is effective in animal models of infection. By increasing the number of agents tested and studying the mode of binding of PDF inhibitors in different bacterial species, it should be possible to improve antibacterial potency against target groups of bacterial pathogens.

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